REMARKS

Applicants submit that the present amendments to the specification do not introduce new matter. For example, on page 9, the sentence has been amended to make more clear which site is close to the enzymatically active site of histone deacetylase. On pages 12 and 13, language has been removed to more accurately describe the process of preparing a cyclic tetrapeptide derivative. On pages 20, 24, 36 and 40, the amendments correct inadvertent errors.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be examined. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

Paragraph beginning at page 9, line 6 has been amended as follows:

In one aspect of the invention, among the above four amino acids, D-configuration may be chosen for the cyclic amino acid represented by general formula (IV), while the remaining three take L-configuration; or D-configuration may be chosen for the amino acids represented by general formulae (II) and (IV), while the remaining two take L-configuration. It should also be noted that in the cyclic peptide of interest, [a site close to the enzymatically active site of histone deacetlyase is not the side chain of N-acetylated lysine, which is an inherent substrate for the enzyme, but hydroxamic acid derived from the side chain carboxyl group in the amino acid of general formula (V),] hydroxamic acid derived from the side chain carboxyl group in the amino acid of general formulae (V) is a site close to the enzymatically active site of histone deacetylase instead of the side chain of N-acetylated lysine, so in one aspect L-configuration is selected for the amino acid of general formulae (V) as in the case of naturally occurring lysine.

Paragraph beginning at page 12, line 12 has been amended as follows:

One-tenth of the amount to be used of the peptide [represented by general formulae (VIII)] is dissolved in DMF and adjusted to a concentration of 0.1 mM. To the DMF solution under ice cooling, a tertiary amine, e.g., diisopropylethylamine and HATU (0-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) is added, and stirred at room temperature for 30 minutes. Subsequently, 1/10 of the amount to be used of the peptide, [represented by general formula (VIII) and] diisopropylethylamine and HATU are added to the above DMF solution and stirred at room temperature for 30 minutes. These procedures were repeated 10 times in total to effect a cyclization reaction. After the reaction, the product (cyclic peptide) is extracted into ethyl acetate and then purified by flash chromatography using a silica gel column.

Paragraph beginning at page 13, line 8 has been amended as follows:

In adition to the above synthesis methods, the above compounds may also be synthesized by methods utilizing solid phase synthesis [as illustrated in the below mentioned Examples].

Paragraph beginning at page 13, line 11 has been amended as follows:

A pharmaceutically acceptable salt of the cyclic tetrapeptide derivative according to the present invention means, for example, a salt with a pharmaceutically acceptable inorganic acid, such as hydrochloride, and a salt with a pharmaceutically acceptable organic acid, such as acetate [salt], if the derivative has basic nitrogen atoms.

Paragraph beginning at page 20, line 16 has been amended as follows:

In the following examples, abbreviations for non-naturally occurring amino acids mean the following amino acid residues:

Aib: 2-aminoisobutyric acid:

Asu(NHOH): 2-amino-[-8-hydroxamideoctanedioic acid]7-N-hydroxycarbanoylheptanoic acid;

Acc5: 1-aminocyclopentane-1-carboxylic acid;

Acc6: 1-aminocyclohexane-1-carboxylic acid;

Acc7: 1-aminocycloheptane-1-carboxylic acid;

Acc8: 1-aminocyclooctane-1-carboxylic acid;

1Ain: 1-aminoindane-1-carboxylic acid;

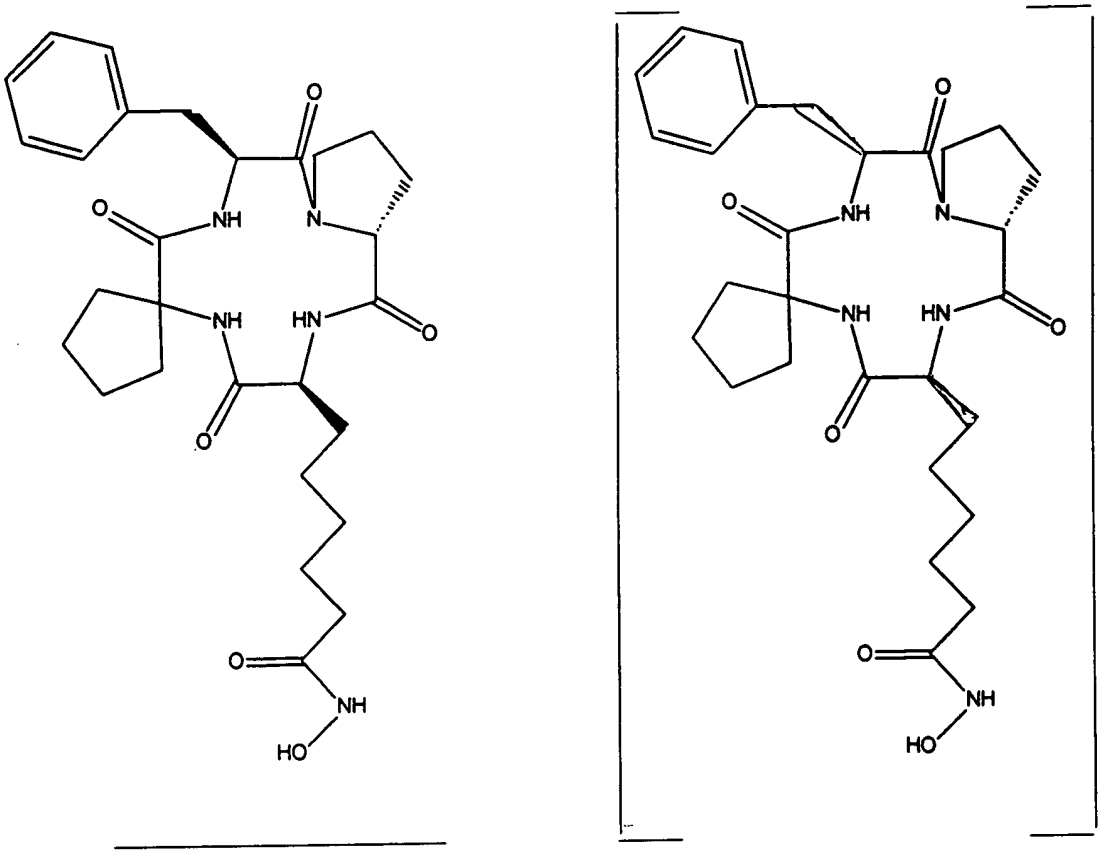
2Ain: 2-aminoindane-2-carboxylic acid;

Pip: pipecolic acid;

Cha: [amino]cyclohexylalanine.

Paragraph beginning at page 24, line 11 has been amended as follows:

Example 1: Synthesis of CHAP-54; cyclo(-L-Asu(NHOH)-Acc5-L-Phe-D-Pro-)



Paragraph beginning at page 36, line 9 has been amended as follows:

Step 7: Cyclo(-L-Asu(OH)-D-Cha-L-Ile-D-Pip-) and cyclo(-L-Asu(OH)-D-Cha-L-Ile-[D],L-Pip-)

Paragraph beginning at page 36, line 26 has been amended as follows:

Step 8: Cyclo(-L-Asu(NHOH)-D-Cha-L-Ile-D-Pip-) and cyclo (-L-Asu(NHOH)-D-Cha-L-Ile-[D,]L-Pip-)

Paragraph beginning at page 40, line 15 has been amended as follows:

Said B16/BL6 cells were inoculated on a 96-well microplate at a cell density of 5000 cells per well, each well containing 200μl of said medium. After culturing for 24 hours, 10μl of a sample containing a given amount of the stock solution of a test compound which had been diluted in the medium was added and cultured for additional 72 hours. Thereafter, each well was washed once with PBS (phosphate buffered saline) and floating cells and the medium were removed. Then, the well was treated with 0.1% glutaraldehyde solution for 3 minutes to fix the cells.